REMARKS

Claims 57-60 and 76-78 are pending in the subject application. No claim has been added, canceled or amended herein. Accordingly, claims 57-60 and 76-78 will still be pending and under examination after consideration of this Communication.

The Claimed Invention

This invention is based on certain surprising discoveries by applicants. Applicants discovered that (i) RAGE-amphoterin is a molecular checkpoint regulating tumor invasion, growth and movement, (ii) a causal link exists between RAGE-amphoterin interaction and tumor invasion, and (iii) the RAGE-amphoterin pathway is not bypassed by a collateral or compensatory pathway.

Specifically, claims 57-60 and 76-78 provide a method for identifying an agent which inhibits tumor invasion in a local cellular environment. This method comprises: (a) providing a solid support coated with amphoterin; (b) contacting the solid support with a tumor cell which expresses receptor for advanced glycation endproducts (RAGE) under appropriate cell culture conditions for cell migration and growth; (c) admixing to the tumor cell culture of step (b) an agent to be tested; (d) determining the amount of spreading of the tumor cells on the solid support; and (e) comparing the amount of spreading of the tumor cells determined in step (d) with the amount of spreading determined in an identical tumor cell culture in the absence of the agent, wherein a decrease in the amount of spreading determined in step (d) indicates that the agent is identified as an agent which inhibits tumor invasion

in the local cellular environment.

Rejection under 35 U.S.C. §103(a) and the September 8, 2005 Examiners' Interview

In the Final Office Action, and as maintained in the Advisory Action, the Examiner rejected claims 57-60 and 76-78 under 35 U.S.C. §103(a) as allegedly obvious over Hori, et al. (J. Biol. Chem. 1995; 270(43):25752-25761) ("Hori") in view of Miki, et al. (Biochem. Biophys. Res. Commun. 1993 Oct. 29:196(2):984-9) ("Miki") and Parkkinen, et al. (J. Bio. Chem. 1993 Sept. 268(26):19726-19738) ("Parkkinen").

Applicants respectfully traverse this rejection.

In order to find the subject application obvious over Hori in view of Miki and Parkkinen, the prior art references, in combination, must teach or suggest all the elements thereof, and create both a motive to combine and a reasonable expectation of success. Hori, Miki and Parkkinen fail to do this.

Applicants maintain that prior to their surprising discoveries described above, one of ordinary skill in the art would not have reasonably expected that inhibiting RAGE-amphoterin interaction would inhibit tumor invasion. Thus, it follows that one of ordinary skill in the art would not have reasonably expected the claimed method to succeed.

During the September 8, 2005 telephonic interview, the undersigned attorney, Alan J. Morrison, and the Examiners assigned to this

application discussed this rejection. Applicants wish to thank the Examiners for their time and consideration. During the interview, the Examiners indicated that this rejection could be overcome were applicants to submit evidence persuasively showing the unexpected nature of applicants' finding that inhibiting RAGE/amphoterin interaction inhibits tumor invasion.

Accordingly, and in support of their position that such finding is unexpected, applicants attach hereto as **Exhibit 1** a Declaration under 37 C.F.R. §1.132 of Ann Marie Schmidt, M.D., a co-inventor named in the subject application. In the Declaration, Dr. Schmidt establishes the following:

1. She is a co-author of the article entitled "Blockade of RAGE-amphoterin signalling suppresses tumour growth and metastases" (Taguchi, et al., Nature 405:354-360 (2000)) ("Taguchi"), annexed to the Declaration as **Exhibit B**, and Taguchi describes certain experimental findings incorporated into the subject application, namely, that RAGE-amphoterin interaction is a pathway for tumor invasion and that this pathway is not bypassed by a compensatory or collateral pathway.

2. She is also familiar with the article entitled "Cancer: Checkpoint for Invasion" (Liotta and Clair, Nature 405:287-288 (2000)) ("Liotta"), annexed to the Declaration as **Exhibit C**, and understands that Liotta is a review of the findings set forth in Taguchi. In the first paragraph, Liotta states, in part, that "Taguchi and colleagues. . . have now identified proteins called

RAGE and amphoterin as a receptor-ligand pair in a molecular checkpoint that regulates not only the invasiveness but also the growth and movement of tumour cells - the trio of characteristics required for malignancy." She understands this statement to mean that prior to the findings in Taguchi, *it was not known that RAGE-amphoterin is a molecular checkpoint regulating tumor invasion, growth and movement*.

3. She also understands the statement in the fourth paragraph of Liotta, which recites, in part, that "the best way to link a molecule causally to malignancy is to start with a cell that is already malignant, and to attempt to block the molecule or pathway of interest. This was the tack taken by Taguchi et al" to mean that prior to the findings of Taguchi, *no causal link was known to exist between RAGE-amphoterin interaction and tumor invasion*.

4. She also understands the statement in the last paragraph of Liotta, which recites, in part, that "[t]he trick is to find a rheostat in the cell's circuitry that is not bypassed by collateral or compensatory paths" to mean that prior to the findings set forth in Taguchi, *it was not established that the RAGE-amphoterin pathway is not bypassed by a collateral or compensatory pathway*.

In sum, not until applicants' findings was the specific role of the RAGE-amphoterin pathway in tumor invasion elucidated. Prior to their discovery of this specific role of RAGE/amphoterin in tumor

invasion, there could have been no reasonable expectation, in view of the cited references, that inhibiting RAGE-amphoterin interaction would inhibit tumor invasion. It follows that the cited references create no reasonable expectation of success regarding the claimed methods. To maintain otherwise would constitute hindsight.

Accordingly, applicants maintain that the subject claims are not obvious over Hori in view of Miki and Parkinnen, and therefore satisfy the requirements of 35 U.S.C. §103(a).

Summary

For the reasons set forth hereinabove, applicants respectfully request that all the claims of this application be allowed, and that the application proceed to issuance.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee, other than the $395.00 RCE filing fee and the $60.00 fee for a one-month extension of time, is deemed necessary in connection with the filing of this Communication. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:

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Alan J. Morrison Date
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